REMARKS

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

I. Status of the claims

No claims are added, amended or canceled in this paper. Accordingly, claims 1, 2, 5, 8-12, 14-19, 22 and 23 are pending, with claims 1, 2 5, 8-11, 18, 19, 22 and 23 under examination.

II. Claim rejection – 35 U.S.C. § 103(a)

Claims 1, 2, 5, 8-11, 22 and 23 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 02/058721 to Margolin ("Margolin"), and further in view of U.S. Patent Publication No. 2003/0165875 to Colonna ("Colonna"). Applicants respectfully traverse this ground for rejection.

The pending claims relate to methods of diagnosing sepsis or pneumonia of bacterial or fungal origin in a subject. The methods include the steps of measuring *soluble* TREM-1 receptor levels in the subject, comparing the measured levels with control levels, and correlating *elevated levels* in the subject with the presence or extent of the disease. The combination of references does not teach or suggest using *soluble* TREM-1 receptor for the diagnosis of bacterial or fungal sepsis or pneumonia, as required by Applicants' claimed invention.

A. Margolin

Margolin describes both the membrane-bound form of TREM-1 and a soluble form of TREM-1 having amino acid sequence of SEQ ID NO: 2 ("TREM-1 splice variant"). Margolin at page 3, line 2 and paragraph [0009]. With respect to diagnostic methods, Margolin describes "a method of diagnosing an inflammatory response" or an autoimmune disease by measuring the level of membrane bound TREM-1 on monocytes and/or the level of TREM-1 splice variant in the blood. *See e.g.*, paragraphs [0018]-[0020], [0084], [0165]. Per Margolin, an *increase* in the

level of membrane-bound TREM-1 is indicative of an inflammatory response, while a *decrease* in the level of soluble TREM-1 splice variant is indicative of an inflammatory response. *Id.*

Margloin also describes methods of treating or modulating an inflammatory response by administering the soluble TREM-1 splice variant. *See e.g.*, paragraphs [0012]-[0017]. Margolin describes that the disease or condition to be treated can include infectious disease, such as septic arthritis or septic shock. Margolin at paragraph [0107]. However, Margolin *does not* teach or suggest a method of diagnosing sepsis or pneumonia of bacterial or fungal origin by measuring soluble TREM-1 levels.

B. Colonna

Colonna relates to methods and compositions including TREM-1 and TREM-2, both transmembrane (*i.e.*, membrane bound) glycoproteins. Per Colonna, TREM-1 is "expressed selectively on blood neutrophils and a subset of monocytes...and is upregulated by bacterial and fungal products," while TREM-2 is "expressed selectively on mast cells and peripherial dendritic cells (DC's)...and has strong utility in modulating host immune response in various immune disorders." Colonna at abstract.

Colonna describes that the naturally-occurring membrane-bound form of TREM-1 is *insoluble*. For example, Colonna states that "[i]n the case of cell-free assays comprising the membrane-bound form of the polypeptide, it may be desirable *to use a solubilizing agent* such that the membrane-bound form of the polypeptide is maintained in solution." *See* Colonna at paragraph [0225]. Thus, this form of TREM-1 is not "inherently" soluble.

Colonna also describes generating a soluble form of TREM-1 by creating a fusion protein between TREM-1 and IgG1. *See e.g.*, Colonna at paragraphs [0278], [0281], [0304]-[0305]. In various experiments, Colonna introduces this fusion into mouse to determine its potential as a prophylactic or treatment; however, this administered polypeptide clearly cannot be used to diagnose a disease or disorder such as pneumonia or sepsis.

While Colonna broadly describes diagnostic and prognostic assays involving the detection of TREM-1 or TREM-2 polypeptides or polynucleotides (*see e.g.,* Colonna at paragraphs [0244]-[271]), Colonna does not disclose diagnosing bacterial or fungal pneumonia or sepsis by detecting the *soluble* form of TREM-1; in particular, *Colonna does not disclose this form of TREM-1 at all*.

C. The combination of Margolin and Colonna does not render the pending claims obvious because Margolin teaches away from the claimed methods

Only Margolin teaches the soluble form of TREM-1, and any diagnostic correlations disclosed in Margolin related to this form of the protein are the *opposite* of what is shown in the present application and of what is claimed. Colonna does not cure this deficiency.

With respect to the membrane-bound, insoluble form of TREM-1, both Margolin and Colonna teach that an *increase* in the level of this protein on monocytes or neutrophils is indicative of an inflammatory response. *See e.g.*, Margolin at paragraph [0018], [0020], and *see e.g.*, Colonna at a paragraph [0274]. With respect to the soluble form of TREM-1, Margolin teaches that a *decrease* in the level of soluble TREM-1 is indicative of an inflammatory response. *See e.g.*, Margolin at paragraph [0019]-[0020]. As noted above, Colonna is silent with respect to the soluble form of TREM-1.

The teachings of Margolin are in direct contrast to the data presented in the present specification. For example, Example 2 clearly demonstrates that an *increased* level of soluble TREM-1 ("sTREM-1") in patient bronchoalveolar lavage samples is indicative of pneumonia, *see e.g.*, data at page 32. Likewise, Example 3 demonstrates that in *increased* level of sTREM-1 in patient sample plasma samples indicates sepsis, *see e.g.*, data at page 40.

Accordingly, there is no reason the skilled artisan, after having read Margolin and Colonna, would "obviously" develop a method of diagnosing bacterial or fungal pneumonia or sepsis by determining sTREM-1 levels, yet alone develop diagnostic methods which correlate *elevated* sTREM-1 levels with the presence or extent of the disease.

For at least these reasons, the rejection under 35 U.S.C. § 103 is improper, and reconsideration and withdrawal is respectfully requested.

III. Conclusion

Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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